

## REVIEW ARTICLE

# Peritoneal Fibrosing Syndrome: Pathogenetic Mechanism and Current Therapeutic Strategies

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Peritoneal dialysis (PD) has been established as a main renal replacement therapy for approximately 20 years. However, long-term peritoneal exposure to high glucose and other unphysiologic contents in the PD solution may potentiate the development of peritoneal fibrosing syndrome (PFS) in PD patients. PFS is composed of a wide spectrum of peritoneal alterations, which has been observed in PD patients. Molecular studies have shown that the fibrogenic effect of peritoneal mesothelial cells and the accompanying accumulation of extracellular matrix in the peritoneum are key events leading to PFS. In this review, we highlight the impact of PFS and its pathogenetic factors, including bioincompatible PD solution, multidisciplinary inflammatory mediators, and stimulatory cytokines in the peritoneal cavity. Current therapeutic strategies based on both clinical and basic evidence for the prevention or treatment of PFS are also reviewed. [*J Chin Med Assoc* 2005;68(9):401–405]

**Key Words:** cyclic AMP, dipyrindamole, fibrosis, mesothelial cell, pentoxifylline

## Introduction

Peritoneal dialysis (PD) has been established as a major mode of renal replacement therapy for approximately 20 years.<sup>1</sup> Due to its convenience in ambulation and an equivalent patient survival as with hemodialysis, there are more than 130,000 patients who have received PD therapy around the world.<sup>2</sup> Despite an improvement in uremic care, however, up to half of PD patients drop out within 5 years of starting therapy in the USA.<sup>3</sup> In a small-cohort survey of local patients, we found that 16% of PD patients experienced technical failure in the first 2 years of therapy.<sup>4</sup> Although acute peritonitis remains the most frequent complication of PD, in our patients, the leading cause of drop-out was ultrafiltration failure,<sup>4</sup> which most likely results from changes in the peritoneal membrane secondary to glucose exposure<sup>5</sup> or to bioincompatible PD solution.<sup>6</sup>

A collective term, peritoneal fibrosing syndrome

(PFS), is used to represent a wide range of structural changes in the human peritoneum that is observed in long-term PD patients.<sup>7</sup> The most common form of PFS is simple peritoneal sclerosis (SS), which has a low clinical impact but high prevalence in long-term PD patients. At the other extreme is encapsulating peritoneal sclerosis (EPS), which is relatively rare but has a high mortality.<sup>8</sup> In this review, we describe the basic mechanisms and clinical implications of PFS, with special emphasis on therapeutic strategies.

## Why is the issue of PFS important?

PFS is common in uremic patients who regularly undergo PD. In a large-cohort study on the morphologic changes in the peritoneal membrane of PD patients, Williams et al<sup>9</sup> found that nearly 61% of the biopsy samples exhibited fibrosis. They also identified a high prevalence of vasculopathy in some

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severe cases. Regarding EPS, a Japanese cohort study of 6,923 patients from 130 centers demonstrated a prevalence of 0.9%.<sup>10</sup> A similar survey performed in Australia reported an EPS incidence of 2% after 2 years of PD, which increased to 19% after 8 years of PD.<sup>11</sup> Although the incidence of EPS is relatively low in PFS patients, the mortality rate is high (20–93%); 60% of patients die within 4 months of diagnosis.<sup>8,10,11</sup> Thus, nephrologists caring for PD patients need to understand the mechanisms underlying PFS and potential therapeutic strategies for its prevention.

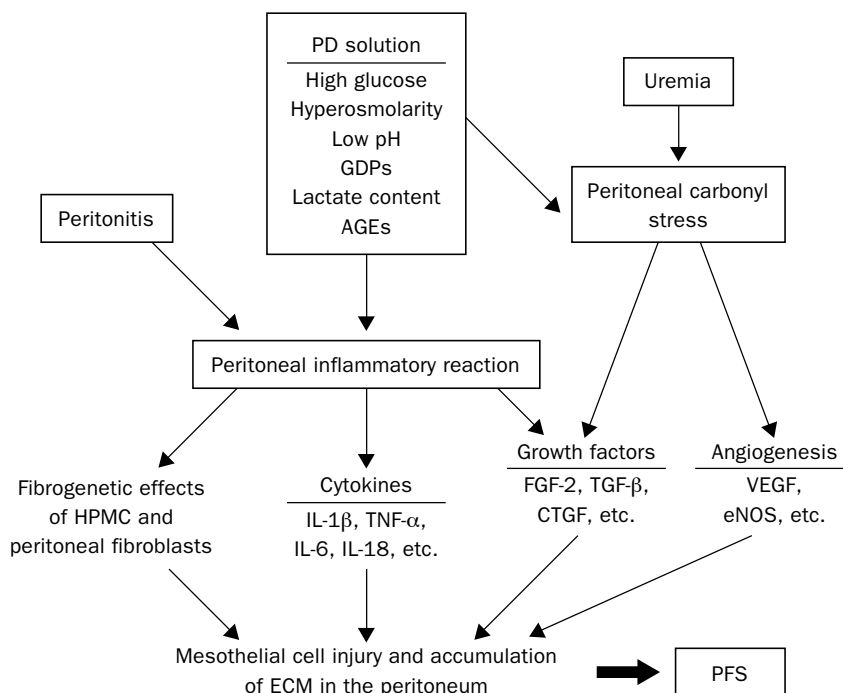
## Epidemiologic Analysis of Risk Factors

The best way to explore any possible therapeutic intervention for a disease is to understand the disease's pathogenetic mechanisms and risk factors. Over the past few years, studies using human and experimental models have elucidated the pathogenesis of PFS. Acute peritonitis<sup>12</sup> and chronic exposure to high glucose<sup>5,13</sup> and bioincompatible PD solutions<sup>6,14</sup> are the leading risk factors for the development of PFS. Furthermore, Williams et al<sup>6</sup> reported a weak but positive correlation between episodes of peritonitis and the thickness of the submesothelial layer in their cohort. They also observed that changes in the thickness of the submesothelial compact zone correlated with the

development of vasculopathy, neoangiogenesis, and total glucose exposure of the peritoneum.

## Molecular Mechanisms in PFS Pathogenesis

A brief summary of proposed factors involved in the development of PFS is shown in Figure 1. Uremia, *per se*, induces peritoneal carbonyl stress and accelerates the formation of advanced glycosylation end products (AGEs).<sup>15</sup> Peritoneal inflammatory reaction, continuously stimulated by PD solutions and amplified through episodic peritonitis, is the central process mediating the pathogenesis of PFS.<sup>7,16</sup> Under these complex co-stimulatory conditions, peritoneal mesothelial cells (PMC), together with other peritoneal cell populations (peritoneal fibroblasts, macrophages, monocytes, neutrophils) and their cytokine products, all contribute to the subsequent development of PFS.<sup>7</sup> Accordingly, the main pathogenetic mechanisms mediating the development of PFS are the inadequate over-proliferation of PMC and/or peritoneal fibroblasts and the accumulation of extracellular matrix (ECM). In this review, therefore, we focus on research regulating the cellular proliferation and matrix production of the peritoneum, with the aim of exploring possible therapeutic strategies for the prevention or retardation of PFS.



**Figure 1.** Possible molecular mechanisms leading to the development of peritoneal fibrosing syndrome (PFS) in patients on peritoneal dialysis (PD). AGEs = advanced glycosylation end products; CTGF = connective tissue growth factor; ECM = extracellular matrix; eNOS = endothelial cell nitric oxide synthase; FGF = fibroblast growth factor; GDPs = glucose degradation products; HPMC = human peritoneal mesothelial cells; IL = interleukin; TGF = transforming growth factor; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

## Current Therapeutic Strategies

The most promising approach for preserving peritoneal membrane integrity is the development and clinical application of more biocompatible PD solutions.<sup>7,15,17,18</sup>

Glucocorticoid, with its attenuation effect on local inflammatory reactions, has been tried since 1993, with some success in patients with PFS.<sup>19</sup> However, concerns on issues of patient safety and the usage of immunosuppressants during or immediately after bacterial peritonitis remains under debate.

Tamoxifen, an estrogen-receptor antagonist, has been reported to be successful in the treatment of many fibrosing diseases, such as retroperitoneal fibrosis, fibrosing mediastinitis and sclerosing cervicitis. Although the molecular mechanism by which tamoxifen prevents fibrogenic reactions remains unclear, del Peso et al<sup>20</sup> reported a successful experience with tamoxifen in the treatment of PFS.

Gene therapy, based on the rationale of possibly genetically modifying the peritoneal membrane, has been applied for preserving membrane longevity.<sup>21-23</sup> These approaches for PFS prevention seem promising. However, the usefulness and long-term effect of this high-tech therapeutic strategy for preservation of the peritoneal membrane remains undetermined.

Along with the increased popularity of PD, an increased incidence of PFS and a growing prevalence of peritoneal changes in PD patients is expected. Searching for other therapeutic agents for the prevention and/or retardation of PFS is mandatory.

## Rationale of Dipyridamole and Pentoxifylline for PFS

Dipyridamole and pentoxifylline have long been used clinically as antiplatelet agents.<sup>24</sup> Both agents act as phosphodiesterase inhibitors that increase intracellular cyclic adenosine 3',5'-monophosphate (cAMP). It has been reported that cAMP-raising agents may inhibit cellular proliferation<sup>25</sup> and attenuate ECM accumulation.<sup>26</sup> We previously demonstrated, in rat mesangial cells<sup>27-29</sup> and vascular smooth muscle cells,<sup>30</sup> that agents increasing intracellular cAMP inhibit cell proliferation and suppress collagen synthesis. We, therefore, hypothesized that dipyridamole or pentoxifylline, through elevated intracellular cAMP, may have similar effects on PMC.

Platelet-derived growth factor (PDGF)<sup>31,32</sup> and transforming growth factor- $\beta$  (TGF- $\beta$ )<sup>33-35</sup> are the main factors mediating cell growth and ECM accumulation, respectively. Recently, it was found that

the mitogen-activated protein kinase (MAPK) family<sup>32</sup> and Smad pathway<sup>33-35</sup> are key factors mediating intracellular signaling of PDGF and TGF- $\beta$ . cAMP had been demonstrated to block activation of the MAPK family<sup>36</sup> and Smad pathway<sup>37</sup> secondary to growth factor stimulation in numerous mammalian cells, but it has not yet been studied in PMC. We believe that if dipyridamole and pentoxifylline can suppress cell proliferation as well as collagen gene expression in PMC, the suppression would most likely result from their modulation of intracellular signaling.

### *In vitro studies*

We first examined the effects of pentoxifylline on cell proliferation and collagen synthesis of PMC under stimulation of serum. We found that pentoxifylline not only suppressed serum-stimulated PMC proliferation, but also inhibited TGF- $\beta$ -induced collagen gene expression of PMC.<sup>38</sup> Similar observations have been demonstrated in human peritoneal mesothelial cells (HPMC) when dipyridamole was added *in vitro*.<sup>39</sup> As cell proliferation is driven by cell-cycle machinery, we further studied the cell-cycle regulation of PMC under stimulation with serum or PDGF. We demonstrated that dipyridamole inhibited PMC proliferation through suppression of RB protein phosphorylation and prevention of p27<sup>kip1</sup> ubiquitination.<sup>40</sup> These molecular observations may serve as an important pharmacologic basis for dipyridamole as a therapeutic agent for PFS.

Next, we studied the intracellular signaling pathways of TGF- $\beta$  in PMC and found that Smad2, p38-MAPK, and the extracellular signal-regulated protein kinase (ERK1/2) were activated by TGF- $\beta$ .<sup>41,42</sup> TGF- $\beta$ -stimulated collagen  $\alpha$ 1(I) and  $\alpha$ 1(III) mRNA expression of HPMC was inhibited by dipyridamole in a dose-dependent manner. Dipyridamole suppressed ERK1/2 activation by TGF- $\beta$ ; in contrast, dipyridamole had no effect on TGF- $\beta$ -induced activation of Smad2.<sup>41</sup> We believe that dipyridamole inhibits TGF- $\beta$ -induced collagen gene expression in PMC mainly through modulation of the ERK pathway. Pentoxifylline, through modulation of p38-MAPK and ERK1/2 activation, prevented collagen gene expression in TGF- $\beta$ -treated PMC.<sup>42</sup>

### *In vivo studies*

What we observed *in vitro* does not necessarily happen *in vivo*. However, based on the low incidence of EPS and the long time duration leading to the development of PFS in humans, we need to establish appropriate animal models for *in vivo* experiments. We have successfully developed 2 animal models: a silica-induced

PFS model,<sup>43</sup> and a bacterial peritonitis-related PFS model.<sup>39</sup> The former depends largely on the roles of peritoneal fibroblasts, and the latter on the behavior of PMC. The therapeutic potential of dipyridamole and pentoxifylline in the prevention of PFS was demonstrated *in vivo*.

## Conclusion

It had been postulated by Williams et al,<sup>9</sup> through a long-term clinical survey, that a variable degree of PFS develops in nearly every patient after varying durations of PD therapy. PFS may lead to a gradual decrease in PD efficiency.<sup>3</sup> Through these *in vitro* and *in vivo* studies, we elucidated the specific inflammatory and/or fibrogenic processes leading to the development of PFS, which may also aid in the development of therapeutic strategies for the prevention or treatment of PFS.

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